466224 PMID: 15505412

Apoptosome dysfunction in human cancer.

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Apoptosis is a cell suicide mechanism that enables organisms to control cell number and eliminate cells that threaten survival. The apoptotic cascade can be triggered through two major pathways. Extracellular signals such as members of the tumor necrosis factor (TNF) family can activate the receptor-mediated extrinsic pathway. Alternatively, stress signals such as DNA damage, hypoxia, and loss of survival signals may trigger the mitochondrial intrinsic pathway. In the latter, mitochondrial damage results in cytochrome c release and formation of the **apoptosome**, a multimeric protein complex containing Apaf-1, cytochrome c , and caspase-9. Once bound to the **apoptosome** , caspase-9 is activated, and subsequently triggers a cascade of effector caspase activation and proteolysis, leading to apoptotic cell death. Recent efforts have led to the identification of multiple factors that modulate **apoptosome** formation and function. Alterations in the expression and/or function of these factors may contribute to the pathogenesis of cancer and resistance of tumor cells to chemotherapy or radiation. In this review we discuss how disruption of normal **apoptosome** formation and function may lead or contribute to tumor development and progression.

6469178 PMID: 15648737
Hypothermia inhibits Fas-mediated apoptosis of primary mouse hepatocytes in culture.
Fu Tao; Blei Andres T; Takamura Noriaki; Lin Tesu; Guo Danqing; Li Honglin; O'Gorman Maurice R; Soriano Humberto E
Department of Pediatrics, Northwestern University Feinberg School of Medicine and Children's Memorial Institute for Education and Research, Chicago, IL 60611, USA. t-fu@northwestern.edu
Cell transplantation (United States) 2004, 13 (6) p667-76, ISSN 0963-6897 Journal Code: 9208854
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Document type: Journal Article
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Apoptosis occurs during the isolation and even short-term storage and culture of hepatocytes, and in the pathogenesis of liver diseases, such as hepatic failure and hepatitis. Therapeutic hypothermia has beneficial effects in experimental models of fulminant hepatic failure. The mechanisms underlying the potential benefits of mild hypothermia on the liver have not been well investigated. We examined the effects of temperature on soluble Fas ligand-induced apoptosis in freshly isolated mouse hepatocytes. Decreasing the culture temperature from 37 degrees C to 32 degrees C produced significant suppression of Fas-mediated apoptosis in cultured hepatocytes over a 12-h period. This observation was supported by cell morphology, flow cytometry analysis of cellular DNA content, and Annexin V-FITC staining of membrane phosphatidylserine translocation. In hypothermic conditions, Fas-mediated cytochrome c release from mitochondria of hepatocytes and the proximate downstream activation of caspase-9 were suppressed under mild hypothermic conditions. Effector caspase-7 activity was also inhibited at 32 degrees C. In contrast, the activation of initiator caspase-8 and cleavage of Bid were not affected after Fas-ligand stimulation. These findings suggest that mild hypothermia suppresses Fas-mediated apoptosis of liver cells by the partial inhibition of signaling events including mitochondrial damage, cytochrome c release, and subsequent **apoptosome** formation and effector caspase activation.

... by the partial inhibition of signaling events including mitochondrial damage, cytochrome c release, and subsequent **apoptosome** formation and effector caspase activation.

1/3,K,AB/7
DIALOG(R)File 155:MEDLINE(R)

16466224 PMID: 15505412
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Department of Obstetrics and Gynecology, University of Michigan Medical School, L4000 Women's Hospital, 1500 East Medical Center Drive, Ann Arbor, MI 48109, USA.
Apoptosis - an international journal on programmed cell death (United States) Nov 2004, 9 (6) p691-704, ISSN 1360-8185 Journal Code: 9712129
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM

Type I and type II reactions in TRAIL-induced apoptosis -- results from dose-response studies.

Rudner Justine; Jendrossek Verena; Lauber Kirsten; Daniel Peter T; Wesselborg Sebastian; Belka Claus
Department of Radiation Oncology, University of Tuebingen, Hoppe-Seyler-Str. 3, Tuebingen D-72076, Germany.

Oncogene (England) Jan 6 2005, 24 (1) p130-40, ISSN 0950-9232
Journal Code: 8711562
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Document type: Journal Article
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Main Citation Owner: NLM
Record type: MEDLINE; Completed

Death receptor-induced apoptosis is paradigmatically mediated via the recruitment of FADD adapter molecule to the ligand/receptor complex and subsequent activation of caspase-8. However, several observations provided evidence that components of the mitochondrial apoptosis pathway are involved in death receptor-mediated apoptosis. In this regard, caspase-8-mediated activation of Bid induces the release of cytochrome c from the mitochondria, which, in turn, triggers the formation of the **apoptosome** protein complex, resulting in the activation of caspase-9. Whereas Bax or Bak were shown to be required for the proapoptotic effect of Bid, Bcl-2 was described to interfere with its action. Up to now, contradictory results regarding the role of Bcl-2 in TRAIL-induced apoptosis have been published. In order to study the influence of Bcl-2 on TRAIL-induced cell death more detailed, we utilized a tetracycline-regulated Bcl-2 expression system in Jurkat T cells. After having analysed the dose response for TRAIL-induced activation of caspase-8, -9, -3, breakdown of the mitochondrial membrane potential, and changes in the apoptotic morphology in cells expressing different Bcl-2 levels, we conclude that overexpression of Bcl-2 mediates a partial resistance towards lower doses of TRAIL that can be overcome when higher doses of TRAIL are applied. Thus, the requirement of the mitochondrial pathway for death receptor-induced apoptosis in type II cells should be reconsidered, since the protective effect of Bcl-2 is limited to lower TRAIL doses or early observation time points.

... release of cytochrome c from the mitochondria, which, in turn, triggers the formation of the **apoptosome** protein complex, resulting in the activation of caspase-9. Whereas Bax or Bak were shown...

1/3,K,AB/4
DIALOG(R)File 155:MEDLINE(R)

17272855 PMID: 15523899

Immunocytochemical detection of members of the caspase cascade of apoptosis in high-grade astrocytomas.

Bodey Bela; Bodey Vivian; Siegel Stuart E; Nasir Aejaz; Coppola Domenico; Hakam Ardeshir; Kaiser Hans E
Department of Pathology, University of Southern California, Keck School of Medicine, Los Angeles, CA, USA. Bodey18@aol.com

In vivo (Athens, Greece) (Greece) Sep-Oct 2004, 18 (5) p593-602, ISSN 0258-851X Journal Code: 8806809
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH

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*File 155: Medline has been reloaded; acession numbers have changed.
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17281804   PMID: 15632278
  Caspase-dependent and -independent neuronal death: two distinct pathways
to neuronal injury.
  Stefanis L
  Department of Neurology and Pathology, Columbia University, USA.
ls76@columbia.edu
  Neuroscientist - a review journal bringing neurobiology, neurology and
psychiatry (United States)   Feb 2005, 11 (1) p50-62, ISSN 1073-8584
Journal Code: 9504819
  Publishing Model Print
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: In Process
  Caspases are cysteine proteases that mediate apoptotic death in a variety
of cellular systems, including neurons. Caspases are activated through
extrinsic or intrinsic pathways. The latter is used by most neurons in most
situations. In this pathway, release of mitochondrial cytochrome c into the
cytoplasm induces formation of the apoptosome, which leads to the
activation of caspase 9 and subsequently other caspases. Recent data
demonstrate that when caspase activation is inhibited at or downstream of
the apoptosome, neurons undergo a delayed, caspase-independent death.
Furthermore, there are instances, most notably following excitotoxic injury
and calcium overload, in which the direct cell death pathway elicited
differs from classical apoptosis. The molecular and biochemical features of
such caspase-independent, nonapoptotic forms of neuronal death are just
beginning to be elucidated, but alterations at the level of the
mitochondria and noncaspase proteases play significant roles. Mitochondrial
alterations in caspase-independent death may include energy depletion,
generation of free radicals, opening of the permeability transition pore,
and release of cytotoxic proteins, such as apoptosis-inducing factor. The
particular mechanisms employed can be context dependent. In disease states,
in which a combination of apoptotic and nonapoptotic death occurs,
therapeutic strategies need to take into account both caspase-dependent and
-independent pathways.

  ... In this pathway, release of mitochondrial cytochrome c into the
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